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Protection against Haloperidol by Catatoxic Steroids

HANS SELYE and SANDOR SZABO

Institut de médecine et de chirurgie expérimentales
Université de Montréal, Montreal, Canada

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Abstract. Experiments on rats show that the effect of haloperidol upon central nervous system activity is abolished or inhibited by pregnenolone-16α-carbonitrile (PCN), "Catatoxic Steroid Number 1" (CS-1), ethylestrenol, spironolactone, norbolethone, oxandrolone, prednisolone and, to a lesser extent, by progesterone. On the other hand, triamcinolone and thyroxine actually increase the sensitivity of the rat to haloperidol so that normally well-tolerated doses induce a high mortality.

Since the protective effect of the above-mentioned steroids against most toxicants is ascribed to hepatic microsomal enzyme induction, it is of special interest that phenobarbital—one of the most potent nonsteroidal hepatic microsomal enzyme inducers—fails to protect the rat against haloperidol.

These findings confirm earlier observations which showed that there are great qualitative differences between the protective effects of various enzyme inducers upon diverse substrates.

Key words: Haloperidol — Catatoxic Steroids — Phenobarbital — Thyroxine.

Numerous observations have shown during the past few decades that, in addition to their classic functions as regulators of reproduction and general metabolism, the steroids also play a decisive role in determining the resistance of the body against the most varied types of injury. In this respect, they can be classified according to their mechanism of action into two main groups: (a) "syntoxic" steroids which improve tissue tolerance by permitting a "symbiotic" type of coexistence with the pathogen (e.g., by suppressing nonspecific inflammatory or allergic reactions against it) and (b) "catatoxic" steroids which actually destroy the aggressor (e.g., through the induction of hepatic microsomal or other enzymes). The syntoxic effects are virtually limited to glucocorticoids, whereas the catatoxic properties appear to be quite independent of any other known steroid hormone action. The voluminous literature on the defensive role of hormones has been reviewed at length in a recent, extensive monograph (Selye, 1971).

It is noteworthy that various anesthetics and sedatives are particularly amenable to inactivation by catatoxic steroids such as spirono-

lactone, ethylestrenol, norbolethone, oxandrolone, PCN (pregnenolone-16α-carbonitrile) or CS-1 (Catatoxic Steroid Number 1). Thus, it was shown that, in rats, spironolactone pretreatment protects against the anesthetic effect of progesterone, desoxycorticosterone, hydroxydione sodium, methyprylon and pentobarbital (Selye, 1969; Selye, 1970a; Selye *et al.*, 1969a). Norbolethone offers protection against the anesthetic effect of certain compounds (progesterone, desoxycorticosterone, pregnanedione, dehydroepiandrosterone, testosterone, pentobarbital and methyprylon) but does not significantly alter the corresponding actions of other drugs (urethan, diazepam, chlorpromazine, reserpine, phenoxybenzamine, chloral hydrate, potassium bromide or magnesium chloride) (Selye *et al.*, 1969b).

In view of the important neurophysiologic and behavioral actions of butyrophenones, especially haloperidol, we wanted to establish to what extent these depend upon metabolic processes controlled by hormones and particularly by catatoxic steroids.

It will be recalled that haloperidol was introduced for the treatment of psychoses because many of its pharmacologic actions resemble those of piperazine-substituted phenothiazines. The drug is primarily concentrated in the liver and eliminated through the bile and urine (Jarvik, 1970). It has been suggested that butyrophenones, including haloperidol, might act by mimicking γ-aminobutyric acid and blocking the action of glutamic acid, particularly in the extrapyramidal systems. A blockade of the central effect of catecholamines, including dopamine and norepinephrine, has also been demonstrated (Janssen, 1967).

Materials and Methods

Female ARS/Sprague-Dawley rats (Madison, Wisc., U.S.A.) with an initial body weight of 100 g (range 90—110 g) were maintained exclusively on Purina Laboratory Chow and tap water, divided into 15 groups and treated as outlined in Table 1. To obtain the best catatoxic effect, it is important to allow a few days of pretreatment; hence, all animals received haloperidol, p.o. (10 mg/100 g body weight in 0.2 ml DMSO, through a stomach tube) on the fourth and fifth day of treatment with the potentially catatoxic substances.

The following steroids were tested for possible protective or sensitizing effects:

PCN [3β-Hydroxy-20-oxo-5-pregnene-16α-carbonitrile (Searle)],

CS-1[1] [9α-Fluoro-11β,17-dihydroxy-3-oxo-4-androstene-17α-propionic acid potassium salt (Searle)],

1 For Catatoxic Steroid Number 1. Manufacturer's code number: SC-11927.

Ethylestrenol (Organon),
Spironolactone (Searle),
Norbolethone (Wyeth),
Oxandrolone (Searle),
Prednisolone acetate (Roussel),
Triamcinolone (Lederle),
Progesterone (Schering),
Estradiol (Roussel),
Desoxycorticosterone acetate (Schering),
Hydroxydione sodium hemisuccinate (Pfizer).

For comparative purposes, we also tested thyroxine, since it had previously been shown to aggravate digitoxin poisoning (Selye, 1970b), and to antagonize the catatoxic effect of various steroids upon several other substrates (Selye, 1971). Finally, phenobarbital, a classic non-hormonal microsomal inducer, acted as a control substance.

All steroids were administered at the dose level of 10 mg in 1 ml water, p.o., twice daily, throughout the period of observation. Thyroxine (B.D.H.) was injected subcutaneously (in the form of its sodium salt) at the dose of 200 μg in 0.2 ml water, once daily, and phenobarbital sodium (B.D.H.) at the dose of 6 mg in 1 ml water, p.o., twice daily, on the same day as the steroids.

Table 1 lists the mean intensity of the motor disturbances characteristic of haloperidol intoxication in the rat, as expressed in an arbitrary scale in which 0 = no change, 1 = just detectable motor incoordination, 2 = inability to walk, 3 = loss of righting reflex. However, for statistical evaluation, we recognized only two grades: minor and sometimes dubious degrees of motor disturbances (between "0" and "1" in our scale) were rated as negative, all others as positive. The motor disturbances were registered on the 5 th day, 3 h after the last haloperidol injection, and mortality was listed on the 7 th day. The statistical evaluation was performed according to the "Exact Probability Test" of Fisher and Yates (Finney, 1948; Siegel, 1956).

Results

As shown by Table 1, the haloperidol-induced motor disturbances were highly significantly prevented by PCN, CS-1, ethylestrenol, spironolactone, norbolethone, oxandrolone and prednisolone. Progesterone offered a somewhat less pronounced but still significant protection, whereas the other steroids, as well as thyroxine and phenobarbital, proved to be ineffective. In fact, triamcinolone and thyroxine actually sensitized the rats to the toxic effects of haloperidol as judged by the highly significant mortality induced by the drug at a dose level at which no mortality was observed in the controls.

Table 1. *Protection against haloperidol by catatoxic steroids*

Treatment[a]	Dyskinesia[b] (positive/total)	Mortality[b] (dead/total)
None	14/15	0/15
PCN	0/10***	0/10 NS
CS-1	0/10***	0/10 NS
Ethylestrenol	2/10***	0/10 NS
Spironolactone	0/10***	0/10 NS
Norbolethone	1/10***	0/10 NS
Oxandrolone	2/10***	0/10 NS
Prednisolone acetate	0/10***	0/10 NS
Triamcinolone	8/10 NS	8/10<u>***</u>
Progesterone	4/10**	1/10 NS
Estradiol	10/10 NS	0/10 NS
Desoxycorticosterone acetate	8/10 NS	0/10 NS
Hydroxydione	6/10 NS	0/10 NS
Thyroxine	10/10 NS	10/10<u>***</u>
Phenobarbital	9/10 NS	0/10 NS

[a] The rats of all groups were given haloperidol as described in the text.

[b] *** $P < 0.005$; ** $P < 0.01$, * $P < 0.05$. Plain asterisks indicate inhibition, underlined asterisks aggravation of toxicity.

Discussion

From these observations, it is clear that all the known active catatoxic steroids (PCN, CS-1, ethylestrenol, spironolactone, norbolethone and oxandrolone) are highly potent in protecting the rat against haloperidol intoxication. Prednisolone is equally potent in this respect but this effect cannot be ascribed to its glucocorticoid activity since triamcinolone, a much more powerful glucocorticoid, not only failed to protect but actually increased sensitivity to haloperidol. It is known that, although prednisolone and progesterone have rather limited catatoxic effects, they do protect the rat against certain toxicants, owing to pharmacologic properties which appear to be quite independent of their glucocorticoid and luteoid effects respectively (Selye, 1971).

That thyroxine has an effect opposite to that of catatoxic steroids is likewise not unexpected in view of earlier observations on the antagonism between thyroid hormones and defensive steroids (Selye, 1970b). It is noteworthy, however, that phenobarbital—one of the most active nonsteroidal microsomal enzyme inducers, which offers protection against numerous toxicants—proved to be quite ineffective against haloperidol toxicity. It may be concluded that if the effect of catatoxic steroids depends upon the induction of hepatic microsomal enzymes—as suggested by many observations on substrate clearance and enzyme activa-

tion using other drugs (for literature see monograph: Selye, 1971)—there must exist considerable qualitative differences between the steroid and the phenobarbital type of induction. We share this point of view, and numerous findings confirming it have been discussed elsewhere (Selye, 1971).

The observations reported here are in agreement with earlier findings concerning the great variations in the "activity spectrum" of catatoxic steroids and drugs. However, further research will be needed to elucidate the metabolic pathways whose regulation is responsible for this great diversity of defensive mechanisms. In any event, it is clear that under certain conditions, the effect of drugs upon higher nervous activity is considerably influenced by the hormonal milieu of the organism.

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Dr. Hans Selye
Institut de Médecine et de Chirurgie expérimentales
Université de Montréal
Montreal 101, Quebec
Canada